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SELECT: THE NEXT PROSTATE CANCER PREVENTION TRIAL

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ABSTRACT

Purpose: Growing evidence implies that selenium and vitamin E may decrease the risk of prostate cancer. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a randomized prospective double-blind study designed to determine whether selenium and vitamin E decrease the risk of prostate cancer in healthy men.

Materials and Methods: The preclinical and epidemiological evidence regarding chemoprevention with selenium and vitamin E were reviewed. Secondary analyses from randomized trials of the 2 agents were included in the current analysis. Data from these analyses as well as evidence from the Prostate Cancer Prevention Trial were used to develop the SELECT schema.

Results: Preclinical, epidemiological and phase III data imply that selenium and vitamin E have potential efficacy for prostate cancer prevention. The experience of the Prostate Cancer Prevention Trial shows the interest and dedication of healthy men to long-term studies of cancer prevention. A total of 32,400 men are planned to be randomized in SELECT.

Conclusions: SELECT is the second large-scale study of chemoprevention for prostate cancer. Enrollment in the study is planned to begin in 2001 with final results anticipated in 2013.

KEY WORDS: prostate, prostatic neoplasms, chemoprevention, selenium, vitamin E

Prostate cancer has been the most common visceral malignancy in American men for the last decade. The estimated lifetime risk of disease is 16.6% for white and 18.1% for black men with a lifetime risk of death of 3.5% and 4.3%, respectively.[1] The dramatic increase in the number of cases and steady increase in mortality from prostate cancer, which has only recently begun to decrease, have peaked interest in developing ways of preventing disease. The recognition that androgens are important for prostate cancer led to the Prostate Cancer Prevention Trial (PCPT) (Southwestern Oncology Group-9217) with finasteride. The PCPT is an ongoing, phase III, double-blind, placebo controlled, randomized trial to determine the efficacy of finasteride for decreasing the period prevalence of prostate cancer. The PCPT opened in 1993 and easily exceeded the goal of 18,000 randomized men during a 3-year accrual period. Final results of this trial are expected in 2003.

Recent research indicates that selenium and vitamin E are promising candidates for prostate cancer prevention based primarily on secondary analysis of large-scale chemoprevention trials in other types of cancer.[2,3] The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is an intergroup phase III, randomized, double-blind, placebo controlled, population based clinical trial designed to test the efficacy of selenium and vitamin E alone and in combination for preventing prostate cancer.

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RATIONALE FOR STUDY AGENTS

Selenium. Selenium is a nonmetallic trace element recognized as a nutrient essential to human health. Selenium is an essential constituent of at least 4 extracellular and cellular glutathione peroxidases, 3 thyroidal and extra-thyroidal iodothyronine 5′deiodinases, thioredoxin reductase, and other selenoproteins. The typical dietary intake of selenium in the United States is 80 to 120 $\mu g.$ daily and the recommended dietary allowance is 0.87 $\mu g./kg.$[4]

Selenium inhibits tumorigenesis in various experimental models.[5] Of the more than 100 reported studies in more than 2 dozen animal models two-thirds have shown decreased tumor incidence in response to selenium supplementation. Male rats pretreated with the chemical carcinogen 3,2′-dimethyl-4-aminobiphenyl and fed an antioxidant rich diet that included selenium did not show a decrease in the incidence of prostate cancer compared with controls.[6] However, selenium has been shown to inhibit the growth of DU-145 human prostate carcinoma cells in vitro.[7] A number of potential mechanisms have been proposed to explain the antitumorigenic effects of selenium, including antioxidant effects, enhancement of immune function, induction of apoptosis, inhibition of cell proliferation, alteration of carcinogen metabolism, cytotoxicity of metabolites formed under high selenium conditions and an influence on testosterone production.[8–14]

Human Observational Studies: Epidemiological evidence indicates that selenium status may be inversely related to the risk of at least some types of cancer, including gastrointestinal malignancy and prostate cancer.[5] In a recent nested case-control study the risk of advanced prostate cancer was decreased by half to two-thirds in men with the highest selenium status.[15]

Controlled Intervention Trials. Two large randomized trials have shown findings relevant to selenium supplementation and cancer.[16,17] In the Nutrition Intervention Trial of

more than 29,000 individuals 40 to 69 years old from the general population of Linxian, China 50 μg. selenium daily with 30 mg. vitamin E and 15 mg. β-carotene daily led to a 13% decrease in mortality from cancer at all sites and a 21% decrease in mortality from stomach cancer. In the second trial done in Linxian investigators tested the hypothesis that a multivitamin/mineral, including 50 μg. selenium plus 15 mg. β-carotene daily would decrease the risk of esophageal/gastric cardia cancer in a population of more than 3,000 individuals with esophageal dysplasia.[17] In this population total cancer mortality was 7% lower and esophageal cancer was 14% lower in the supplemented group. The independent effect of selenium and impact of supplementation on prostate cancer was not evaluated in these trials because of the trial design and small numbers of cases in the study population.

Recent enthusiasm for selenium for preventing prostate cancer arose after publication of the results of the clinical trial of Clark et al.[3] In this series 1,312 patients with a history of skin cancer were randomized to receive 200 μg. elemental selenium daily in the form of selenized yeast or placebo. They were followed an average of 4.5 years for basal or squamous cell carcinoma of the skin and other cancer. While no difference was noted in the rate of skin cancer, further analysis revealed that the prostate cancer incidence was decreased by two-thirds in men in the selenium supplemented group. Based on a small number of cases additional stratified analysis suggested a greater decrease in prostate cancer in men with low baseline selenium, those younger than 65 years and those with low serum prostate specific antigen (PSA).[18] There also were significant reductions in the incidence of lung and colon cancer in this trial.[15]

Vitamin E (α-tocopherol). Vitamin E is a family of naturally occurring, essential, fat soluble vitamin compounds. Its importance in mammalian biology was initially shown by earlier fertility research.[19] Vitamin E, which functions as the major lipid soluble antioxidant in cell membranes, is a chain breaking, free radical scavenger that inhibits lipid peroxidation, specifically biological activity relevant to carcinogen induced DNA damage.[20] α-Tocopherol, the most active form of vitamin E, is also one of the most abundant, and it is widely distributed in nature and the predominant form in human tissue.[21,22]

α-Tocopherol may influence cancer development through several mechanisms. It has a strong inherent potential for antioxidating highly reactive and genotoxic electrophiles, such as hydroxyl, superoxide, lipid peroxyl and hydroperoxyl, as well as nitrogen radicals, thereby, preventing the propagation of free radical damage in biological membranes and decreasing mutagenesis and carcinogenesis.[20] Vitamin E also blocks nitrosamine formation. α-Tocopherol inhibits protein kinase C activity, and the proliferation of smooth muscle cells and melanoma cells.[23–26] Vitamin E also induces the detoxification enzyme decreased nicotinamide adenine dinucleotide phosphate:quinone reductase in cancer cell lines and inhibits arachidonic acid and prostaglandin metabolism.[27,28] Effects on hormones that can increase cellular oxidative stress and proliferative activity as well as on cell mediated immunity have also been reported.[28]

Studies indicate that vitamin E inhibits the growth of certain human cancer cell lines, including melanoma, oral carcinoma, and those of the prostate, lung, and breast, while animal experiments have shown the prevention of various chemically induced tumors, including hormonally mediated lesions.[29–32] In these studies vitamin E has also slowed the growth of prostate tumors in vitro and in vivo in rats receiving various doses of chemotherapeutic agents. The average dietary vitamin E intake in men and women in the United States is estimated to be 10 and 7 mg. daily, respectively.[33,34] The recommended daily dietary allowance of the National Research Council is 10 and 8 mg. for men and women, respectively.[34]

Human Observational Studies: Evidence currently implies that vitamin E status or intake is inversely related to the risk of lung and colorectal cancer. In 4 of 6 cohort studies of lung cancer prediagnostic serum vitamin E was lower in cases in which cancer subsequently developed compared with noncases and 1 showed no differences in baseline dietary intake in cases and noncases or a weakly protective association for supplemental vitamin E.[35–37] In 2 other cohorts vitamin E intake was not associated with lung cancer.[38,39] In 5 prospective studies the association of serum α-tocopherol and colorectal cancer was evaluated. Generally serum levels were lower in cases in which colorectal cancer subsequently developed compared with noncases and a pooled estimate of a 40% lower risk has been reported for the highest versus lowest category of serum α-tocopherol concentration.[40] In contrast, prospective studies have indicated no association of dietary vitamin E intake with the incidence of colon or colorectal cancer, although a study in women in Iowa showed a 50% decrease in the colon cancer incidence for vitamin E supplement use and an estimated relative risk of 0.32 for the highest versus lowest quintile of vitamin E intake from diet plus supplements.[41,42] A case-control study in Italy showed a significant inverse association for higher vitamin E intake or for 200 IU or greater daily versus none, while findings in several others revealed no substantive relationship with colorectal cancer.[43–46]

Observational studies are inconsistent with regard to a beneficial association of serum vitamin E with prostate cancer. These studies assessed cancer risk through estimated dietary intake, or plasma or serum α-tocopherol measurement. In 2 of the few prospective studies with a sufficient number of prostate cancer cases for analysis no dose response association was noted and in 1 there was a statistically significant protective association.[47–49] A study of 2,974 subjects with a 17-year followup indicated that low α-tocopherol is associated with higher prostate cancer risk.[50] In all studies there was a lower serum or plasma vitamin E concentration in prostate cancer cases years before diagnosis.[48–50] A cohort analysis showed that the associations of prostate cancer with baseline serum and dietary α-tocopherol differed significantly according to α-tocopherol intervention status with the suggestion of a protective effect for total vitamin E intake in men who also received α-tocopherol supplementation.[51] Another case-control study demonstrated no association of vitamin E intake with prostate cancer risk.[52]

Controlled Intervention Trials: Large-scale, randomized, placebo controlled trials support the role of vitamin E for preventing prostate cancer. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) Study was done in Finland, and the Nutrition Intervention Trials I and II were performed in China. The ATBC Study was a randomized, double-blind, placebo controlled trial of α-tocopherol in the form of 50 mg. synthetic dl-α-tocopherol acetate daily and 20 mg. β-carotene daily alone or in combination in 29,133 male smokers 50 to 69 years old at study entry.[2,53] During the median followup of 6.1 years there were 246 new cases of prostate cancer and 64 deaths from prostate cancer. Of the 14,564 patients assigned to the α-tocopherol supplementation arm of the trial there were 99 incident prostate cancers compared with 147 in the 14,569 assigned to the non-α-tocopherol arm, representing a statistically significant 32% decrease in the prostate cancer incidence (95% confidence interval [CI] 12 to 47; $p = 0.002$).[2] The observed preventive effect appeared stronger in clinically evident cases, that is stages B-D disease, that received α-tocopherol, in which the incidence decreased 40% (95% CI −20 to −55). Although prostate cancer mortality data are based on fewer events, they indicated a similarly strong effect of 41% lower mortality (95% CI −1 to −64). Although prostate cancer was prespecified as a secondary end point in this trial, these findings

imply a potentially substantial benefit of α-tocopherol for decreasing the risk of prostate cancer.

SELECT

SELECT is a double-blind, placebo controlled, 2 × 2 factorial study of selenium and vitamin E alone and in combination in 32,400 healthy men with a digital rectal examination not suspicious for cancer and serum prostate specific antigen (PSA) 4 ng./ml. or less (see figure and appendix 1). Age eligibility is 55 years in white and 50 years in black men since 50 to 55-year-old black American men have a prostate cancer incidence rate comparable to that of 55 to 60-year-old white men. Randomized men are planned to be equally distributed among the 4 study arms (see figure). Intervention consists of a daily oral dose of study supplement and/or matched placebo according to randomization (see figure). Study duration is planned to be 12 years with a 5-year uniform accrual period, and a minimum of 7 and maximum of 12 years of intervention depending on the time of randomization.

The study supplements include 200 μg. l-selenomethionine, 400 mg. racemic α-tocopherol and an optional multivitamin containing no selenium or vitamin E. L-selenomethionine was chosen over selenized yeast on the advice of a National Cancer Institute sponsored panel of experts. The recommendations were based on marked batch-to-batch variability in various forms of selenium in the selenized yeast used in the Clark et al trial, lack of commercial availability of the selenized yeast used in the Clark et al trial[3] and laboratory analysis that determined that the predominate selenium species in currently commercially available selenized yeast is l-selenomethionine. The racemic mix of α-tocopherol includes the d and l-isomers.

Study end points. The primary end point of the trial is the clinical incidence of prostate cancer on a recommended routine clinical diagnostic evaluation, including yearly digital rectal examination and serum PSA measurement. A centrally reviewed histological diagnosis of prostate cancer is required in all cases except those based on total PSA greater than 50 ng./ml. and positive bone scan. Prostate biopsy is planned to be performed at the discretion of study physicians according to local community standards. The study protocol recommends biopsy for study participants with digital rectal examination suspicious for cancer and/or elevated serum PSA. Unlike the PCPT no biopsy is required at the end of SELECT. Secondary end points are prostate cancer-free survival, all cause mortality, and the incidence and mortality of other types of cancer and disease potentially impacted by the chronic administration of selenium and vitamin E (appendix 2). Other trial objectives include periodic quality of life assessment, serum micronutrient measurement and prostate cancer risk, and the evaluation of biological and genetic markers associated with the risk of prostate cancer.

Statistical considerations. Sample Size Calculation: The primary study analysis includes 5 pre-specified comparisons, namely 1) vitamin E versus placebo, 2) selenium versus placebo, 3) combined vitamin E plus selenium versus placebo, 4) combined vitamin E plus selenium versus vitamin E and 5) combined vitamin E plus selenium versus selenium. The study design enables the detection of a 25% decrease in the incidence of prostate cancer for selenium or vitamin E alone with an additional 25% decrease for combined selenium and vitamin E compared with either agent alone. The study also allows for the potential interaction of vitamin E and selenium. Additional statistical analysis is planned to include tests for vitamin E versus no vitamin E, selenium versus no selenium and interactions of the 2 agents.

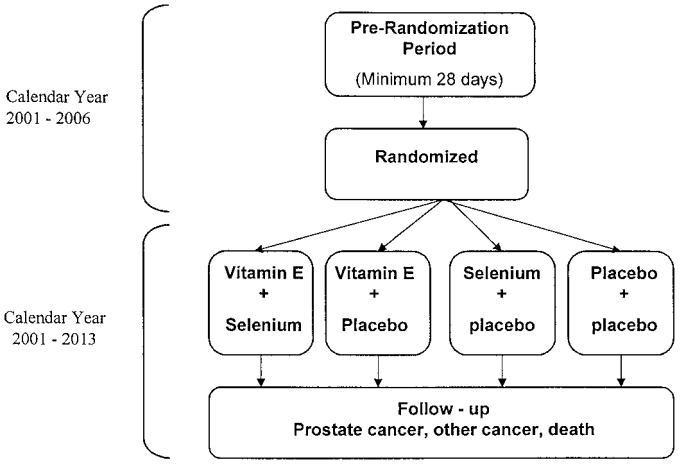
Statistical significance is determined at overall 2-sided α = 5% with each of the 5 comparisons tested at the 1% level to maintain an overall 5% level for the study. With a sample size of 32,400 participants the estimated power for comparing a single agent versus placebo is 96% and the power for comparing an effective single agent versus combined selenium and vitamin E is 89% (table 1). Median time on observation is estimated to be 8.8 years.

Incidence Rate: Based on the PCPT expectations are that participants may be a mean of 63 years old at study entry. The yearly prostate cancer incidence values used in sample size calculations were derived from the observations of the PCPT and Surveillance, Epidemiology and End Result (SEER) databases. The estimated incidence of prostate cancer begins at 0% at randomization, is 0.14% at year 1 and increases steadily to 1.36% at 12 years. Table 2 lists the number of participants with prostate cancer expected in each study arm based on 8,100 participants per arm.

Medication Rate: The medication rate is an estimate of the percent of participants who ingest the study supplements, quantified as the percent of the complete active drug dose ingested by men per arm. It is assumed that the medication rate may vary with time with a decrease from 100% after randomization to 51% at the end of 12 years of treatment. These estimates are based on observed rates in the PCPT. Compliance with daily medication in SELECT may be higher than in the PCPT because finasteride has more side effects than those known for selenium or vitamin E.

Drop-In Rate: The drop-in rate, defined as the rate of participants randomized to placebo who independently obtain and ingest selenium and/or vitamin E, is assumed to be constant at 10% for the 12 years of treatment. Recent Heart Outcomes Prevention Evaluation data support this estimate.[54] A drop-in rate of 15% decreases study power to 92% for comparing placebo to either single agent and 82% for an effective single agent versus the combination.

Competing Death and Loss Risks: The cumulative competing risk is defined as the estimated cumulative all-cause mortality rate plus the cumulative lost to followup rate. The mortality rates were obtained from the PCPT for the initial 4 years of treatment and then adjusted upward to the 1995 American rate for all races. The lost to followup rate was calculated as 0.05%



Schema

TABLE 1. *Power calculations*

Comparison	Baseline Hazard Incidence	% Relative Risk Decrease	% Power
Single agent vs. placebo	PCPT/SEER	25	96
Placebo vs. combination	PCPT/SEER	44	Greater than 99
Effective single agent vs. combination	0.75 × PCPT/SEER	25	89

TABLE 2. *Expected incidence of prostate cancer in each arm under the alternative hypothesis*

	No. (proportion)
Placebo	533 (0.066)
Vitamin E	403 (0.050)
Selenium	403 (0.050)
Vitamin E plus selenium	304 (0.038)

A total of 8,100 participants at risk per arm.

yearly. The cumulative loss (death plus lost to followup) is expected to be 0.8% at the end of study year 1 and 33.2% by the end of year 12.

Other Factors: In contrast to finasteride, it is assumed that the drugs tested in SELECT do not affect PSA or prostate size. Either effect would bias the diagnosis of prostate cancer. PSA at baseline and after 2 years of vitamin E administration have been analyzed in a subsample of participants in the Heart Outcomes Prevention Evaluation trial and after 3 years in the ATBC study.[2,55] There was no evidence of an effect on PSA concentration in these studies.

Differences in SELECT and PCPT. Experience in the PCPT has influenced the design of SELECT. These differences include broader eligibility criteria, elimination of the placebo run-in period, less frequent followup contacts and reliance on community standards for diagnosing prostate cancer (table 3). These changes reflect the larger sample size of SELECT, minimal side effects expected from the study agents and an effort to simplify data management.

CONCLUSIONS

Ample evidence exists in preclinical studies, epidemiological observations, and controlled and uncontrolled clinical trials that selenium and vitamin E may prevent the development or progression of prostate cancer. SELECT is a large-scale, population based, randomized controlled trial that is planned to test directly the effect of these agents alone and in combination on the incidence of prostate cancer in North American men.

APPENDIX 1: STUDY ELIGIBILITY CRITERIA

Patient age
- For white men 55 or older
- For black men 50 or older

Digital rectal examination not suspicious for prostate cancer

Total serum PSA 4 ng./ml. or less

No history of prostate cancer or high grade prostatic intraepithelial neoplasia

No anticoagulation therapy except low dose aspirin

Normal blood pressure with systolic less than 150 and diastolic less than 90 mm. Hg

Willingness to restrict supplementation of selenium and vitamin E during participation

TABLE 3. *Differences in PCPT and SELECT study designs*

Variable	PCPT	SELECT
Agent	Finasteride	1-Selenomethionine, α-tocopherol
Eligibility criteria:*		
Pt. age	55 or Older	50 or older for black men, 55 or older for all others
Total PSA (ng./ml.)	3 or Less	4 or less
Primary end point	7-Yr. prevalence	Incidence
Placebo run-in	Yes	No
Followup	Every 3 mos.	Every 3 mos. yr 1, thereafter every 6 mos.
Disease ascertainment	Biopsy required	Biopsy recommended per community standard
End of study biopsy	Yes	No
Central laboratory facility	All PSA measurements	None
Pathology review	All biopsies	Prostate Ca only
Quality of life studies	All participants	Subset only
Secondary end points	Prostate Ca, screening issues	All Ca issues
% Black male participation	4	Projected 20

* Nonsuspicious digital rectal examination in each study.

APPENDIX 2: STUDY END POINTS

Primary: incident prostate cancer, as determined by routine clinical care

Secondary
- Prostate cancer-free survival
- Overall survival
- Incidence and survival
  - All cancer
  - Lung cancer
  - Colorectal cancer
- Serious cardiovascular events

Other
- Quality of life measures
- Molecular epidemiology
- Dietary nutrient assessment
- Biomarker studies

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